

## Dermatomyositis

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Dermatomyositis is a rare inflammatory myopathy with characteristic skin manifestations and muscular weakness. The disease can be categorized as adult idiopathic, juvenile, or amyopathic dermatomyositis as well as that associated with a connective tissue disease or a malignancy. Immunologic factors are most likely involved in the pathogenesis of the disease; however, genetic and environmental issues may also play important roles. Treatment with immunosuppressive agents has proved successful in the majority of patients, although significant morbidity still occurs. (*J Am Acad Dermatol* 1998;39:899-920.)

**Learning objective:** At the conclusion of this learning activity, participants should be familiar with the clinical characteristics of adult idiopathic, juvenile, and amyopathic dermatomyositis as well as the histopathologic and immunopathologic characteristics of the disease.

### DEFINITION AND CRITERIA

Idiopathic inflammatory myopathies share the histopathologic feature of inflammation in striated muscle. The 3 different types of idiopathic inflammatory myopathies that do not affect neuromuscular transmission are dermatomyositis, polymyositis, and inclusion body myositis. Specific subtypes of the former two categories are detailed in Table I. This article focuses on dermatomyositis with specific mention of polymyositis when appropriate for comparison or elucidation. Amyopathic dermatomyositis is seen in patients who have the typical cutaneous manifestations of dermatomyositis without clinical and/or laboratory findings of muscle involvement for at least 6 months after the onset of the rash. Inclusion body myositis is not discussed because it is a distinct clinical entity that does not mimic the skin or musculoskeletal findings of dermatomyositis.

The classification of polymyositis and dermatomyositis was clarified by a landmark article written by Bohan and Peter<sup>1,2</sup> in 1975. In their descrip-

tion of non-neurogenic myositis, the authors outlined the criteria for dermatomyositis and polymyositis, and assigned a systematic way in which to describe the probability of having the diseases as definite, probable, and possible (Table II). The criteria aid in assessing the likelihood of patients having the disease, provide a standard by which patients can be evaluated, and help to validate patient selection and conclusions deduced from data procured by studies. However, more recent data on myositis-specific antibodies (MSAs) may provide a better categorization scheme for the future evaluation of patients.

### HISTORY OF DERMATOMYOSITIS

Dermatomyositis was first noted in the literature in 1863 when Wagner<sup>3</sup> published a description of a patient with the disease. In the late 19th century 4 authors independently published clinical descriptions.<sup>4-7</sup> The syndrome was coined dermatomyositis, polymyositis, pseudotrichinosis, and myositis universalis acuta infectiosa. Reports in the early 20th century stress the implication that the disease was "a reaction of the reticulo-endothelial system"<sup>8-13</sup> or associated with scleroderma, bacterial and viral infections,<sup>14,15</sup> systemic lupus erythematosus and polyarteritis nodosa,<sup>16,17</sup> thyro-

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**Fig 1.** A pathognomonic manifestation of dermatomyositis, Gottron's papule, is seen overlying proximal interphalangeal joint. Also noted are periungual telangiectases.

toxicosis and myasthenia gravis,<sup>18,19</sup> or vascular disease.<sup>15,20,21</sup> Fifty percent to 60% mortality rates were the norm.

## EPIDEMIOLOGY

Dermatomyositis and polymyositis combined (DM/PM) have incidence and prevalence rates of 1 to 10 and 10 to 60 cases per million population, respectively.<sup>22-29</sup> In juvenile dermatomyositis, the incidence is 1 to 3.2 cases per million children.<sup>30,31</sup> These figures are estimates; the true incidence and prevalence are difficult to ascertain because of the rarity of the disease and the lack of consistent use of diagnostic criteria. Skin manifestations in inflammatory myopathy have been identified in 30% to 40% of adult patients and in 95% of children.<sup>26,32,33</sup> Many studies have found a preponderance of female over male patients, commonly 1.5 to 2.0:1.0 with a higher ratio in DM/PM associated with connective tissue disease and an equal sex ratio in older patients with malignancy.<sup>22,24,34-41</sup> The average age at diagnosis of DM/PM is approximately 40 years, whereas that associated with malignancy is 55 years.<sup>40,42</sup> The average adult age distribution is 45 to 54 years of age, with the lowest rate occurring in 15- to 24-year-old patients.<sup>24,43</sup> Juvenile dermatomyositis has a bimodal age distribution with peaks at 5 to 9 and 10 to 14 years of age. DM/PM associated with a connective tissue disease occurs in younger women with a higher preponderance in African-American persons, whereas white women are predominantly affected with der-

**Table I.** Classification of patients with polymyositis or dermatomyositis

Polymyositis
Dermatomyositis
Juvenile polymyositis or dermatomyositis
Polymyositis or dermatomyositis associated with a connective tissue disease
Polymyositis or dermatomyositis associated with malignancy
Amyopathic dermatomyositis

**Table II.** Diagnostic criteria for dermatomyositis<sup>1,2</sup>

1. Proximal symmetric muscle weakness, progressing weeks to months
2. Muscle biopsy evidence of an inflammatory myopathy
3. Elevation of serum muscle enzymes
4. Electromyographic features of a myopathy
5. Cutaneous eruption typical of dermatomyositis\*

*Definite PM/DM:* Fulfill 4 criteria

*Probable PM/DM:* Fulfill 3 criteria

*Possible PM/DM:* Fulfill 2 criteria

\*Criteria #5 must be one of the stated number of criteria in patients with definite, probable, or possible dermatomyositis.

matomyositis both with and without malignancy.<sup>24,42</sup> Amyopathic dermatomyositis is significantly more common in adults.

## CLINICAL MANIFESTATIONS

### Primary idiopathic dermatomyositis

Skin findings are the distinguishing clinical feature of dermatomyositis relative to polymyositis. The primary, classic skin lesion is a violaceous macular erythema distributed symmetrically. As the disease progresses, the erythema may become progressively poikilodermatous and indurated, the latter secondary to mucin deposition. The pathognomonic skin manifestations, occurring in approximately 70% of patients, include Gottron's papules, which consist of violaceous papules overlying the dorsal interphalangeal or metacarpophalangeal (Fig 1), elbow, or knee joints and Gottron's sign, which consists of erythematous or violaceous, often atrophic macules or plaques in the same distribution. Characteristic skin lesions include periungual telangiectases (Fig 1), the erythematous/lilac heliotrope macular rash with peri-orbital edema that involves the eyelids (Fig 2), and



**Fig 2.** Heliotrope rash manifests as a violaceous erythema overlying upper and sometimes lower eyelids associated with periorbital edema.



**Fig 3.** Erythematous, poikilodermatous macules distributed on the neck, upper back, shoulders, and arms define the shawl sign, which is a characteristic finding in dermatomyositis.

erythematous, poikilodermatous macules distributed in a shawl distribution over the shoulders, arms, and upper back (Fig 3).<sup>44</sup> The heliotrope rash, seen in 30% to 60% of patients, may selectively involve the upper eyelids and may parallel the patient's clinical course.<sup>45</sup> In African-American patients, the periorbital edema may be the only visible finding of the heliotrope rash. Periungual telangiectases are not a specific finding and can be seen in other connective tissue diseases. Erythema on sun-exposed skin is seen in one third of patients, and photosensitivity may be present.<sup>46,47</sup> Other less common skin findings include mechanic's hands (Fig 4; fissured, scaly, hyperkeratotic, and hyperpigmented hands),<sup>48</sup> facial swelling,<sup>49</sup> acquired ichthyosis,<sup>50</sup> cutaneous vasculitis,<sup>51</sup> panniculitis,<sup>52-54</sup> nasal septal perforation,<sup>55</sup> erythroderma,<sup>56,57</sup> lichen planus,<sup>58</sup> porcelain white atrophic scars resembling Degos'

disease,<sup>59</sup> and vesicle or bullae formation.<sup>60-62</sup> Extremely rare associations with dermatomyositis include follicular hyperkeratosis,<sup>63,64</sup> malacoplakia,<sup>65</sup> panniculitis,<sup>66</sup> and papular mucinosis.<sup>67</sup> Pruritus is a common clinical feature. The cutaneous involvement in dermatomyositis sometimes waxes and wanes with treatment but in no way reflects the severity of the associated myositis. Moreover, the skin manifestations can continue to worsen when the muscular manifestations have already been alleviated with treatment.

Muscular involvement in DM/PM includes symmetric weakness that develops over weeks to months in proximal muscles, as evidenced by difficulty walking up stairs, getting up from a chair, or combing one's hair. Dysphagia and fatigue are common symptoms secondary to pharyngeal and neck flexor involvement, and myalgias and muscle tenderness are also reported.<sup>26</sup> The weakness



**Fig 4.** Fissured, scaly, hyperkeratotic hands in patients with myositis are known as mechanic's hands.

waxes and wanes. Deep tendon reflexes are unchanged, and muscular atrophy occurs late in the course of the disease.<sup>1</sup> The weakness is usually progressive but can be acute or gradual. Lumbar lordosis or Trendelenburg gait can also be seen, and the facial and bulbar muscles are usually spared.<sup>23,47</sup> Muscle pain in the acute form of the disease is common.<sup>68</sup> Falling, cardiac palpitations, and muscular atrophy have been reported to be statistically more prevalent in polymyositis than in dermatomyositis.<sup>42</sup> There is no correlation between the extent of skin disease and muscle disease activity.<sup>69</sup> Other organ systems (ie, pulmonary, cardiac, gastrointestinal, ophthalmologic) can also be involved (Table III).<sup>47,70-73</sup> Interstitial lung disease is particularly prevalent (40%-60%) in the group of patients with myositis who have antisynthetase antibodies, commonly referred to as the antisynthetase syndrome (Table IV). Arthralgias are seen in the minority of patients, and the typical joint findings are nonerosive and nondeforming, usually without synovitis.<sup>74</sup> Specific clinical syndromes are associated with particular autoantibodies, and this relationship will be discussed later (see "Laboratory Manifestations").

### Juvenile dermatomyositis

Juvenile dermatomyositis differs from its adult counterpart because of clinical and histologic features.<sup>37</sup> Except for an increased incidence of calcinosis cutis in the younger population, skin lesions are similar to those in adult dermatomyositis. Uncommon skin manifestations in juvenile dermatomyositis include hypertrichosis<sup>75,76</sup> and

### Table III. Noncutaneous manifestations of dermatomyositis

*Respiratory manifestations:* Interstitial lung disease (bronchiolitis obliterans organizing pneumonia, interstitial pneumonia, diffuse alveolar damage), aspiration pneumonia, ventilatory insufficiency, drug-induced reaction (secondary to methotrexate use), malignancy, pleural effusions, opportunistic infection, pulmonary hypertension, spontaneous pneumothorax, pulmonary alveolar proteinosis<sup>71,296</sup>

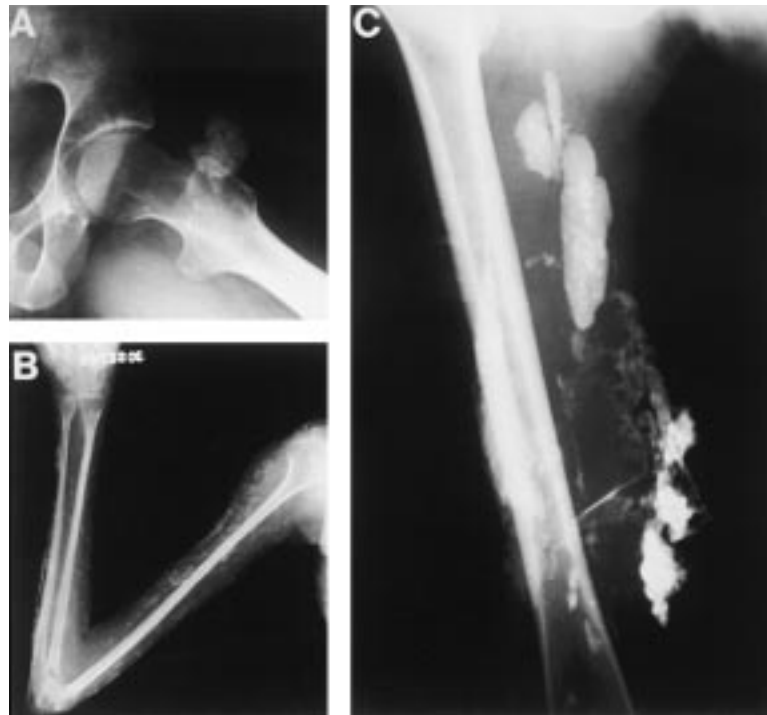
*Cardiac manifestations:* Conduction abnormalities, arrhythmias, myocarditis, congestive heart failure, hyperkinetic state, pericardial tamponade, pericardial effusions, pericarditis<sup>72</sup>

*Gastrointestinal manifestations:* Esophageal reflux, delayed gastric emptying, dysphagia, esophageal dysmotility, decreased intestinal motility, rectal incontinence<sup>70</sup>

*Ocular manifestations:* Conjunctival edema, nystagmus, extraocular muscle imbalance, iritis, cotton-wool spots, optic atrophy, and conjunctival pseudopolyposis<sup>73</sup>

lipoatrophy.<sup>77,78</sup> Low-grade fever is a common symptom, occurring in the majority of patients.<sup>34,35,79</sup> Symmetric arthritis of both large and small joints is common, with joint contractures developing secondary to persistent inflammation and lack of physical therapy. Another study correlated morphologic nailfold capillary bed vasculature with clinical course.<sup>80</sup> Increased gastrointestinal involvement in children manifests as decreased absorption of nutrients, decreased esophageal motility, infarction, ulceration, perforation, hemorrhage, and pneumatosis intestinalis.<sup>30,81,82</sup> Electrocardiographic abnormalities are seen in half of all pediatric cases, manifesting as asymptomatic conduction abnormalities or right bundle branch block, and subclinical, decreased ventilatory capacity is evident in the majority of cases.<sup>81</sup> Gower's sign is seen in juvenile dermatomyositis and reflects truncal weakness.<sup>83</sup> Children placed in the supine position roll over into the prone position and gradually push themselves up with their arms, using their legs as support in an attempt to become erect.

The incidence of calcifications has been reported to be 30%<sup>84</sup> to 70%<sup>85</sup> in the pediatric population compared with less than 10% in adults, and its presentation occurs on the elbows, knees, but-



**Fig 5.** Calcinosis cutis in juvenile dermatomyositis is common. The 4 types include (A) subcutaneous or popcorn-like, (B) superficial, (C) intramuscular in fascial planes, and exoskeleton (not shown).

tocks, or in traumatized areas and is associated with disease duration and activity.<sup>38,86-89</sup> The 4 types of calcium deposition include subcutaneous (also known as tumoral or popcorn-like), superficial, intramuscular in fascial planes, and extensive exoskeleton patterns (Fig 5). In one study attempting to determine the origin of calcinosis cutis in juvenile dermatomyositis,<sup>90</sup> the excretion of  $\gamma$ -carboxyglutamate (the acid form is found in calcinosis cutis) was increased in children with calcinosis relative to both children with juvenile dermatomyositis without calcifications and children with other connective tissue diseases. Another study demonstrated that this calcium-binding amino acid is increased in patients with scleroderma and dermatomyositis and that its level correlates with the extent of calcium deposition.<sup>91</sup> However, oral steroids, the most widely used therapy for the disease, also can cause an increased level of  $\gamma$ -carboxyglutamate, so the results are suspect. Moreover, it is difficult to differentiate the cause and effect of the release of this amino acid. Ironically, a marked reduction in osteocalcin production, a marker of new bone formation, in children who had never been treated with steroids

has also been demonstrated.<sup>92</sup> The levels were increased with the initiation of steroid therapy. There is no association between malignancy and juvenile dermatomyositis; reports of the two occurring together are rare.

#### **Amyopathic dermatomyositis**

Pearson<sup>93</sup> first suggested the term *amyopathic dermatomyositis* (also called dermatomyositis sine myositis) to describe his patients who had the typical, pathognomonic skin changes without muscle weakness or laboratory evidence of muscle involvement. Although most studies do not describe patients with amyopathic dermatomyositis, it has been reported in 2% to 11%<sup>32,41,44,94</sup> of patients with dermatomyositis.<sup>33,95,96</sup> Common complaints from patients with this entity are lethargy and fatigue, pruritus, photosensitivity, and arthralgias. Patients can manifest (1) no clinical or laboratory findings of weakness, (2) clinical signs without laboratory findings, or (3) laboratory findings without clinical signs. This category is controversial in that, by strict Bohan and Peter criteria, patients with this presentation may have improbable dermatomyositis, only fulfilling one criteria.<sup>44</sup>

**Table IV.** Myositis-specific antibodies<sup>42,161,162,297,298</sup>

Autoantibody	Antigen	Frequency in myositis (%)	HLA association
Antisynthetases		20-25	DR3, DRw52, DQA1
Anti-Jo-1	Histidyl-tRNA synthetase		
Anti-PL-7	Threonyl-tRNA synthetase		
Anti-PL-12 [I]	Alanyl-tRNA synthetase		
Anti-PL-12 [II]	Alanyl-tRNA		
Anti-OJ	Isoleucyl-tRNA synthetase		
Anti-EJ	Glycyl-tRNA synthetase		
Anti-SRP	Signal recognition particle proteins	<5	DR5, DRw52, DQA1
Anti-Mi-2	Nuclear helicase	5-10	DRw53, DR7, DQA1
Others			
Anti-FER	Elongation factor 1 $\alpha$		
Anti-KJ	Unidentified cytoplasmic protein		
Anti-MAS	Unidentified cytoplasmic RNA		

Histopathologic findings of the skin rash represent a sensitive but not specific indicator of the disease. Moreover, because the skin changes of the disease can precede the systemic symptoms by years, it is easy to suspect that early, aggressive treatment of the rash with steroids could prevent the consequent myositis, and adequate patient follow-up would be necessary to confirm the diagnosis. It is difficult to assess the probability of systemic manifestations developing in patients with amyopathic dermatomyositis, but cases with lung involvement, such as interstitial lung disease or fibrosing alveolitis, have been reported.<sup>97,98</sup>

Up to one third of patients with primary idiopathic dermatomyositis initially present only with skin changes,<sup>32,44</sup> but characteristic systemic weakness usually develops within 2 years from the onset of the rash, if not earlier.<sup>91-102</sup> A study of 50 patients with dermatomyositis from a referral dermatology practice by Rockerbie et al<sup>103</sup> found that 56% presented with the skin changes only (up to 51 months before weakness), whereas weakness developed in 84% within 6 months of onset of the eruption and 28% had simultaneous skin involvement and muscle weakness. Clinical studies that have included electromyography, determination of serum muscle enzyme levels, and muscle biopsy of patients with amyopathic

dermatomyositis, often demonstrate abnormal results without associated clinical weakness,<sup>32</sup>; however, this is not always the case.<sup>95,104,107</sup> Magnetic resonance imaging (MRI), although an expensive procedure, may be warranted in patients with possible amyopathic dermatomyositis. A study using magnetic resonance imaging and phosphorus-31-labeled magnetic resonance spectroscopy did not demonstrate muscle inflammation at rest but did indicate abnormal muscle metabolism during exercise in two patients with amyopathic dermatomyositis relative to control subjects. Two studies by Stonecipher et al<sup>105,107</sup> demonstrated that 9 of 13 patients without muscle enzyme elevation for 4 to 11 years and 3 of 5 patients with normal findings of muscle enzymes levels, electromyography, and muscle biopsy either went on to manifest muscle changes or had MRI findings of muscular involvement. Antinuclear antibody (ANA) is positive in some patients; however, it is difficult to assess the possibility of systemic lupus erythematosus in patients described in the literature because many of the articles do not describe titer, extractable nuclear antigen results, or a thorough clinical evaluation. Therefore it is important to rule out other possible connective tissue disorders in patients who present only with skin findings.

Clinical associations	Prognosis	
	Response to steroids	5-y survival (%)
Antisynthetase syndrome: Interstitial lung disease, dyspnea, mechanic's hands, arthritis, fevers, Raynaud's phenomenon, carpal tunnel syndrome; polymyositis > dermatomyositis	Moderate	>65
Acute winter onset, severe polymyositis, cardiac palpitations, myalgias	Poor	>30
Classic dermatomyositis, V sign, shawl sign rash, cuticular overgrowth, carpal tunnel syndrome in adults and children	Good	>90
Alcoholic rhabdomyolysis		

### Dermatomyositis associated with a connective tissue disease

A minority of patients with dermatomyositis or polymyositis have an associated connective tissue disease, and this has been reported in 11% to 40% of cases.<sup>22,32,99,108,109</sup> The female-to-male ratio in this subgroup is 9:1. Although muscle involvement is common in connective tissue diseases alone, myalgias and tenderness predominate and the vast majority of patients do not have an inflammatory myopathy.<sup>68</sup> The connective tissue diseases associated with dermatomyositis or polymyositis include mixed connective tissue disease, scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and polyarteritis nodosa. Patients in this category must fulfill the diagnostic criteria of two separate disorders.<sup>110,111</sup> The vast majority of patients with overlap syndrome have polymyositis over dermatomyositis.<sup>32,112</sup> Muscle biopsy specimens of myositis in patients with overlap syndrome may be indistinguishable from that of polymyositis or dermatomyositis<sup>1</sup>; however, often only minimal changes are noted, such as increased interstitial connective tissue, patchy fiber atrophy, focal accumulation of lymphocytes, microcyst formation, sarcoplasmic degeneration, and/or perifascicular atrophy.<sup>113-118</sup>

Whereas patients without an associated connective

tive tissue disease present with muscle weakness and myalgias, those with an associated disease usually present with polyarthritis, Raynaud's phenomenon, sclerodactyly, and sicca syndrome and later develop the traditional symptoms of myositis. In contrast to polymyositis or dermatomyositis, those patients with the overlap syndrome are significantly more likely to have positive, non-myositis-associated antibodies, such as rheumatoid factor, ANA (three fourths of patients with a titer >1:640), double-stranded DNA antibody, Scl-70 antibody, or an extractable nuclear antigen antibody (a majority with RNP antibody and a minority with SS-A and/or SS-B antibody).<sup>22,42</sup> In mixed connective tissue disease, the myositis is usually mild; however, severe symptoms can occur.<sup>103</sup> A study that surveyed hospitalized patients with systemic lupus erythematosus concluded that the incidence of a true inflammatory myopathy was approximately 8%.<sup>119,120</sup> The myositis in patients with overlap syndrome responds better to corticosteroids relative to primary inflammatory myositis.<sup>121</sup>

### DM/PM associated with a malignancy

The concept that either dermatomyositis or polymyositis are paraneoplastic processes has been a controversial subject. The association was

first raised by Stertz<sup>113</sup> in 1916, and since then numerous reports of malignancy-associated disease have been reported.<sup>41,60,94,100,123-132</sup> The controversy stems from the fact that large, controlled, prospective studies have never been done. Thus case reports and smaller, retrospective studies attempting to understand the association between the two diseases and malignancy have often led to erroneous conclusions flawed by referral biases, lack of proper controls, questionable thoroughness in gathering data, lack of sensitivity, diagnostic suspicion bias,<sup>133</sup> poor documentation criteria (mostly before Bohan and Peter's 1975 article), and retrospective review-of-the-literature bias. Understandably, large medical center settings will attract patients who are sicker.<sup>134</sup> Review of hospitalization records implies incorrectly that *all* patients with DM/PM were hospitalized regardless of clinical status. Earlier articles often define patients with either disease based on incomplete analysis of the patients' laboratory or test results and even lack of muscle histopathologic diagnoses. Study coordinators not blinded to patients with disease may order more tests in search of malignancy, and the contrary is also true. A retrospective review of the literature not only compounds the biases described above, but also inaccurately attempts to draw conclusions from a self-selected patient population that does not necessarily reflect the true disease population.<sup>135-140</sup> Disease associated with malignancy would tend to be reported more often than uncomplicated cases. The risk of malignancy in older people is independent of the presence of muscle disease; thus there is a greater chance that DM/PM will be associated with a concurrent neoplasm in older patients (>45 years of age). Amyopathic dermatomyositis has anecdotally been reported to be associated with cancer; no large, controlled studies have been done.<sup>44,105</sup> The inherent difficulty in formulating a stringent epidemiologic study is apparent.

Literature reviews have demonstrated that certain cancers, such as ovarian in women and stomach and lymphoma in men,<sup>141</sup> are highly associated with dermatomyositis and/or polymyositis relative to the normal population.<sup>142</sup> The most common malignancies (eg, breast, lung, or prostate) are often not statistically associated; however, there are conflicting reports. The diagnosis of malignancy can be antecedent, concurrent,

or subsequent to that of DM/PM. Two controlled studies, one of which was population-based,<sup>39</sup> demonstrated no statistically increased rate of malignancy in affected patients.<sup>143</sup> A population-based study from Sweden implied a relative risk of associated malignancy of 1.7 to 1.8 in patients with polymyositis and 2.4 to 3.4 in those with dermatomyositis.<sup>144</sup> Unfortunately, less than 10% of the charts were reviewed to attempt criteria classification, and more than 25% of the patients did not have definite disease. An epidemiologic study in Denmark implied an increased risk of malignancy but did not attempt to confirm or classify the diagnoses.<sup>145</sup> A population-based, retrospective study in Finland, which drew information from nationwide hospitalization records, included only patients with definite polymyositis or dermatomyositis and stated that *all* suspected patients are routinely hospitalized for evaluation.<sup>146</sup> This investigation of 246 patients deduced that there was a 6.5-fold risk of malignancy in patients with dermatomyositis (highest in ovarian, stomach, nonmelanoma skin, lung, and male genital organ cancers), no increased risk in patients with polymyositis, and no increased risk in those patients treated with cytotoxic agents. This is the best study to date that attempts to assess the relation between neoplasia and myositis, and more such studies need to be done to reaffirm the association. The skin and histopathologic findings of adult dermatomyositis associated with malignancy do not differ from those of patients without malignancy.<sup>147,148</sup>

## LABORATORY MANIFESTATIONS

### Muscle enzymes

Muscle enzymes are released when damage to the muscle cell occurs. The following serum muscle enzymes may be elevated in DM/PM: creatine kinase (CK), serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), aspartate aminotransferase (AST), or aldolase.<sup>149</sup> CK catalyzes the formation of adenosine triphosphate and the donation of a phosphate group to creatine, the combination of which is used as a high-energy storage molecule.<sup>150</sup> The most sensitive of the skeletal muscle enzymes, it is found in numerous organs, and the MM subtype is most specific for skeletal muscle.<sup>26</sup> However the CK MB subtype, which is usually seen as a result of cardiac muscle injury,



can be elevated in chronically stressed or regenerating skeletal muscle.<sup>151</sup> Because CK is released after physical exercise or after any trauma to muscle tissue, it is not a specific marker for myositis, although it is the one enzyme most frequently elevated in muscle disease.<sup>152-154</sup> CK is used to follow the clinical course of DM/PM because fluctuations correlate with clinical disease status. These changes can manifest themselves months before or after a change in clinical course, portending improvement or therapy failure.<sup>40,155</sup> CK levels may be normal in patients with concomitant CK activity inhibitors, early in the course of myositis, or after significant muscle atrophy.<sup>156</sup> In healthy African-American males, CK levels may be elevated above the standards used in most testing laboratories.

Aldolase (subtype A),<sup>34,157</sup> an enzyme involved in glycolysis; LDH (isoenzymes 4 and 5), which converts lactate to pyruvate; and the aminotransferases ALT and AST are not sensitive measures of muscle inflammation or response to therapy, but levels can be elevated when the CK is normal in patients with myositis.<sup>35,37,79</sup> Moreover, combining the evaluation of the AST level ( $> 50$  U/L), CK/AST ratio ( $< 40$ ), and CK MB fraction ( $> 2\%$ ) provides a specific and sensitive diagnostic tool to separate polymyositis from other myopathic diseases.<sup>152</sup> Carbonic anhydrase isoenzyme III is found in slow-twitch skeletal muscle and not in the myocardium; thus it is even more specific than LDH or the aminotransferases in the evaluation of myopathies.<sup>158</sup> However, the assay for this enzyme is not widely available.

### Autoantibodies

The antibodies seen in DM/PM can be separated into those that are and those that are not specific for myositis. Of the non-myositis-specific antibodies, low-titer ANA positivity occurs in the majority of cases, despite the absence of associated connective tissue disease.<sup>41,42,159</sup> Those with associated connective tissue disease tend to have higher titer ANAs ( $> 1:160$ ). Anti-RNP, anti-PM-Scl, and anti-Ku antibodies have been associated with myositis in conjunction with overlap syndromes.<sup>160,161</sup> Anti-RNP is associated with the overlap of mixed connective tissue disease or systemic lupus erythematosus and myositis. Patients with anti-Pm-Scl antibody define a unique subset with scleroderma and dermatomyositis or polymyositis.<sup>109</sup> This over-

lap syndrome consists of scleroderma usually limited to the face and hands (including Raynaud's phenomenon), dermatomyositis or polymyositis, nondeforming and nonerosive arthritis, esophageal and lung involvement, and a positive rheumatoid factor. Anti-Ku antibodies are associated with myositis overlap with scleroderma or systemic lupus erythematosus.

MSAs are identified in approximately one third of cases and are seen most commonly in dermatomyositis or polymyositis not associated with a malignancy and less commonly in the other myositic processes.<sup>42,162</sup> These antibodies are directed against certain cytoplasmic proteins and RNA involved in the process of protein synthesis. An individual patient will not express more than one MSA. These antibodies tend to precede the onset of the myositis. It has also been shown that the titers correlate with disease activity and that they tend to disappear after complete remission. There are 4 major groups of MSAs: antibodies targeted against aminoacyl-transfer RNA (tRNA) synthetase; antibodies directed against proteins of the signal recognition particle; antibodies targeted against Mi-2, a nuclear protein complex; and other less common antibodies without clear disease associations.<sup>163</sup> Some authors have advocated the addition of MSA status to the current classification scheme to better characterize the immunogenetic and clinical features of the traditional classification scheme.<sup>42</sup> Table IV lists some of these important associations. Antibodies directed against Mi-2 are highly specific for dermatomyositis, whereas antibodies directed against SRP (signal recognition particle proteins) and MAS (unidentified cytoplasmic RNA protein) are specific for polymyositis. Although seen in half of the patients with dermatomyositis or polymyositis, anti-synthetase antibodies are neither sensitive nor specific for either disease. Antibodies directed against endothelial cells have also been reported, and these patients have a statistically significant increase in interstitial lung disease.<sup>164</sup>

In juvenile dermatomyositis, ANA titers greater than or equal to 1:160 occur in a minority of patients, do not correlate with disease activity at presentation, usually return to normal after successful treatment, and are associated with the presence of immune complexes.<sup>34,35,37,84,165</sup> Relative to controls, patients with juvenile dermatomyositis have an increased incidence of polymyositis (PM-

**Table V.** Pathologic changes of muscle in dermatomyositis and polymyositis<sup>167,299-303</sup>

	Dermatomyositis	Polymyositis
Muscular histopathology	Perivascular, perifascicular inflammation and atrophy, vascular damage, ischemia, segmental fiber necrosis	Fascicular/endomysial inflammation without perifascicular atrophy, necrotic fibers not uniformly distributed
Muscular cytopathology	Higher percentage of B lymphocytes and CD4 <sup>+</sup> lymphocytes	Higher percentage of T lymphocytes T8 <sup>+</sup> cells, and activated T cells with minimal B lymphocyte involvement
Peripheral cytopathology	Decreased CD3 <sup>+</sup> and TLI SA1 <sup>+</sup> mononuclear cells, increased CD20 <sup>+</sup> and CD20 <sup>+</sup> DR <sup>+</sup> cells	Increased CD3 <sup>+</sup> DR <sup>+</sup> mononuclear cells and CD3 <sup>+</sup> DR <sup>+</sup> /DR <sup>+</sup> ratio

1) antibody, a non-myositis-specific antibody. There is no increase in prevalence of either non-specific or specific antibodies in the amyopathic dermatomyositis population.

#### **PATHOLOGY AND IMMUNOPATHOLOGY**

Histopathologic evaluation of skin lesions is similar to that found in cutaneous lupus erythematosus and demonstrates an increased proportion of CD4<sup>+</sup> lymphocytes and HLA-DR<sup>+</sup> macrophages.<sup>166</sup> Hyperkeratosis, vacuolization of the basal keratinocytes, melanin incontinence, perivascular lymphocytic infiltrate, increased dermal edema and mucin deposition, acanthosis, and epidermal atrophy are the characteristic light microscopic findings.<sup>44</sup> Hyperkeratosis is seen in Gottron's papules, whereas poikilodermatous lesions have an atrophic epidermis.

Biopsy findings of involved muscle demonstrates the histopathology outlined in Table V. Histopathologic examination has helped to delineate the pathogenesis of dermatomyositis and to distinguish the mechanism of tissue injury from that of polymyositis and inclusion body myositis. The latter two diseases are most likely a result of cell-mediated cytotoxicity,<sup>28,68,167,168</sup> whereas dermatomyositis involves complement-mediated microvasculopathy.<sup>147,169-175</sup> In lesional skin biopsy specimens of patients with dermatomyositis and those with amyopathic dermatomyositis, but not in patients with systemic lupus erythematosus or subacute systemic lupus erythematosus, significantly increased dermal vascular and dermoepidermal junction C5b-9 complement deposition, vascular fibrin deposition, endothelial injury, and vascular ectasia are seen.<sup>176,177</sup> C5b-9 complement membrane attack complex has been found in the mus-

cle microvasculature in both adult and juvenile dermatomyositis, and the degree of myofibrillar loss correlates with capillary deposits of membrane attack complexes, implying that the disease is secondary to vasculopathy. Those patients with complement deposits detected by muscle biopsy have also been found to have shorter disease duration than those that do not.<sup>172</sup> From a histologic standpoint, there is more consistently severe vascular inflammation and thrombosis in the juvenile cohort relative to adults, and ischemia is most likely the cause of the muscle damage.<sup>147,169,178,179</sup> One study demonstrated a difference in the size of the vessel involved in juvenile dermatomyositis relative to adult dermatomyositis, in that the former had only small-vessel involvement, whereas the latter had small and large (> 20  $\mu$ m) vessels involved.<sup>148</sup> Assays of endothelial damage (factor VIII-related peptide), intravascular thrombosis (fibrinopeptide A), and ongoing complement activation (C3d and C4d) are positive in this patient population.<sup>180-182</sup> Immunofluorescence studies have demonstrated epidermal intercellular immunoglobulin deposits in nailfold biopsy specimens and not in normal skin, but these findings were not found in each patient.<sup>183</sup> Moreover, IgM and C3 can be seen in the vessels of involved skin.<sup>184</sup>

#### **ETIOLOGY**

Genetic factors are likely to play an important role in dermatomyositis, although some studies have failed to link HLA haplotype with disease.<sup>41,42</sup> Studies of histocompatibility antigen prevalence have demonstrated that HLA-B8, HLA-B14, HLA-DR3, HLA-DRw52, and HLA-DQA1 are associated with dermatomyositis,<sup>23,37,47,185-187</sup> and

drug-induced disease is associated with HLA-B18, HLA-B35, and HLA-DR4.<sup>188</sup> Juvenile dermatomyositis is classically associated with HLA-DR3, but in one small study the relative risk of juvenile dermatomyositis developing in persons heterogeneous for HLA-B8 was 11.5.<sup>36</sup>

Immunologic factors most likely are important in the pathogenesis of the idiopathic inflammatory myopathies. Autoantibodies to skeletal muscle myoglobin or myosin in the majority of patients with polymyositis and myositis-specific antigens in those with DM/PM have been discussed earlier.<sup>189,190</sup> Other autoimmune diseases such as Graves disease, systemic lupus erythematosus, Hashimoto's thyroiditis, myasthenia gravis, juvenile diabetes mellitus, dermatitis herpetiformis, and vitiligo have been associated with the inflammatory myopathies.<sup>191</sup> Increased interleukin-2 receptor levels have been found on activated T cells in dermatomyositis or polymyositis.<sup>192-194</sup> Increased peripheral blood mononuclear cell proliferation has been demonstrated in sera when exposed to autologous and homologous muscle homogenates in patients with myositis relative to normal patients as well as to patients with other myopathies or connective tissue disease without a myopathic component.<sup>195</sup>

Environmental factors have been reported to contribute to the cause of inflammatory myopathies as well. Both juvenile and adult forms of dermatomyositis have been associated with infectious agents such as influenza A or B<sup>196-199</sup> and hepatitis B,<sup>200,201</sup> although little scientific evidence has demonstrated a virus as the causative factor.<sup>202</sup> Moreover, elevation of CK values in these patients and clinical symptoms such as myalgia were limited to days. The possible role coxsackie virus plays is intriguing.<sup>203-205</sup> One small study hypothesized that a host response to coxsackie B virus could be related to the pathophysiology of juvenile dermatomyositis, because there was a statistically significant prevalence of complement-fixing coxsackie B viral antibody relative to hospitalized patients with juvenile rheumatoid arthritis and viral syndrome, and this antibody correlated with the course of the illness.<sup>181</sup> Because specific regions of the RNA of an animal picornavirus, the encephalomyocarditis virus, are homologous to one of the myositis-associated antigens (histidyl-tRNA synthetase or Jo-1 antigen) and myosin heavy and light chains, picornaviruses

are logically thought to be possible causes of myositis.<sup>26,163,206,207</sup> One study found that 29 of 58 patients with polymyositis or dermatomyositis had positive serologic titers for the protozoa *Toxoplasma gondii*, whereas patients with systemic lupus and muscular dystrophy did not have an increased prevalence. It is difficult to assess, however, whether *Toxoplasma* is a cause of inflammatory myopathy or whether patients with polymyositis or dermatomyositis are at increased risk of developing this specific protozoan infection. Case reports have suggested an association between dermatomyositis and silicone breast implants; however, this issue remains controversial.<sup>209-211</sup>

### EVALUATION AND DIFFERENTIAL DIAGNOSIS

In patients who present with dermatomyositis or only the skin manifestations of the disease, a thorough history, physical examination, and routine laboratory studies (chest roentgenography, urinalysis, stool guaiac, complete blood cell count with differential, and biochemical screen), electromyography, and muscle biopsy are a necessity. Evaluation of all appropriate muscle enzymes including CK, aldolase, LDH, ALT, and AST is important because elevation of only one enzyme can occur. Any additional tests should be ordered as a result of an abnormal finding of the initial evaluation. Extensive, expensive testing in search of malignancy has proved to be of benefit only when prompted by historical, laboratory, or physical findings.<sup>212</sup> Biopsy is performed on a clinically affected muscle, which is usually a proximal muscle group such as the biceps or quadriceps. Because of the chance of sampling error, MRI can be used to localize an affected area for biopsy; however, some neurologists believe the additional expense may outweigh any benefit. Care must be taken to avoid muscles where electromyography had already been done or where injectable anesthetics have been used, both of which can cause alterations in the histopathologic features.

Electromyography is useful in differentiating a neurogenic from a myogenic process. Electromyography of affected muscles in dermatomyositis demonstrates short, polyphasic motor units, long-duration polyphasic potentials, bizarre, high-frequency repetitive discharges and fibrillation potentials, positive sharp waves, and insertional

irritability.<sup>32,37,112,213-215</sup> MRI can be an independent, contributing factor in the diagnosis of dermatomyositis, especially in patients with normal serum muscle enzymes and lack of proximal muscle weakness.<sup>216</sup> MRI findings of the inflammatory myopathies include subcutaneous edema, increased water content of the muscle secondary to inflammation, intramuscular calcium deposits, and fatty infiltration or atrophy of the muscle.<sup>217-219</sup>

Tests for autoantibodies should be ordered in the appropriate clinical setting, such as ANA and extractable nuclear antigens (SS-A, SS-B, RNP, Sm) in a patient with a suspected overlap syndrome. Myositis-specific autoantibodies theoretically could provide additional information concerning classification and prognosis. Unfortunately, other than the anti-Jo-1 autoantibody, most are available only for research purposes. Patients with amyopathic dermatomyositis should undergo the same tests as those patients with muscle weakness. However, if all tests are negative, an MRI evaluation can be considered. Pending the results, those patients with negative tests and persistence of the rash for more than 2 years have been defined as having confirmed amyopathic dermatomyositis, whereas those patients with the rash for more than 6 months but less than 2 years are defined as having provisional amyopathic dermatomyositis.<sup>220</sup> Periodic clinical examinations and testing of muscle enzymes are warranted in this patient population.

The characteristic skin findings in combination with muscle weakness and appropriate laboratory data can provide straightforward evidence for the diagnosis of dermatomyositis. Unfortunately, many cases do not present in this manner. Differential diagnoses of early skin manifestations of dermatomyositis include polymorphic light eruption, systemic lupus erythematosus, contact dermatitis, lichen planus, seborrheic dermatitis, psoriasis, and atopic dermatitis.<sup>221</sup> Systemic lupus erythematosus can be differentiated from dermatomyositis because the former usually has a higher titer ANA, a positive extractable nuclear antigen test, and less pruritus. The skin manifestations of systemic lupus erythematosus tend to involve the malar eminences more often than the periorbital area and the dorsal surface of the fingers between the joints instead of the surface overlying the joints. The rash in systemic lupus is usually more red or pink as opposed to violaceous, and lupus

myositis is not as severe as that in the inflammatory myopathies.<sup>69</sup> Moreover, as discussed above, biopsy of the dermatomyositis rash demonstrates C5b-9 membrane attack complexes, whereas that of systemic or subacute lupus erythematosus does not. Trichinosis can cause periorbital swelling and edema.<sup>222</sup> HIV infection, usually at the onset of immunodeficiency, can mimic dermatomyositis or polymyositis.<sup>223</sup> As discussed under "Etiology," other viral causes also need to be excluded.

The following drugs have been implicated in producing a characteristic dermatomyositis syndrome: penicillamine,<sup>188,224,226</sup> nonsteroidal anti-inflammatory agents (nifluric acid<sup>227</sup> and phenylbutazone<sup>228</sup>), practolol,<sup>94</sup> hydroxyurea,<sup>229</sup> and pravastatin.<sup>230</sup> Most patients had definite dermatomyositis according to the criteria shown in Table I and had significant muscle involvement; they all had an excellent response to steroid therapy. The symptoms usually began within months of taking the medication, except for penicillamine-induced disease, which in some cases was implicated after 5 to 11 years of therapy. It is almost impossible to rule out primary idiopathic dermatomyositis in these patients, because removal of the drug alone never caused reversal of the syndromes, and most patients underwent a long steroid taper to control the disease.

The differential diagnosis for polymyositis is complex, and the following list is in no way exhaustive: infection; endocrine anomalies such as hypothyroidism, hyperthyroidism, and Cushing's disease; neurologic diseases such as myasthenia gravis, amyotrophic lateral sclerosis, and Guillain-Barre syndrome; metabolic diseases such as hypokalemia, hypocalcemia, and hypophosphatemia; and other drugs such as corticosteroids, alcohol, and zidovudine.<sup>231</sup>

## TREATMENT

Before adequate treatment regimens had been evaluated, roughly equal numbers of patients died, were left severely crippled, and survived the disease without significant sequelae.<sup>8</sup> Some studies reported a 50% mortality rate.<sup>11,232</sup> Regardless of treatment modality, all patients with myositis and/or calcinosis require extensive physical therapy to prevent joint contractures and disuse atrophy of muscle tissue.<sup>26</sup> This may include gentle, passive stretching and splinting in the initial stages of the disease and more aggressive strength building

once the muscle inflammation has subsided.<sup>84</sup> Topical therapy consists of routine sunscreen use for photosensitive patients and class I or II steroids for the pruritus and inflammatory erythematous skin changes. Treatment of calcinosis cutis is extremely difficult, and only anecdotal reports of diltiazem,<sup>233,234</sup> probenecid,<sup>235</sup> warfarin,<sup>236</sup> aluminum hydroxide suspension,<sup>237</sup> EDTA,<sup>238</sup> and colchicine<sup>239</sup> have been published. Surgical debridement of calcifications can offer relief in patients who have decreased range of motion.<sup>240</sup>

### Corticosteroids

Oral steroids are the initial pharmacologic agent for the treatment of dermatomyositis and polymyositis. The justification for steroid usage involves the probable cytotoxic mechanism of polymyositis, the involvement of immune complexes and complement in dermatomyositis, the presence of autoantibodies in many patients, and the association of inflammatory myopathies with collagen vascular diseases.<sup>241</sup> Oral prednisone, 0.5 to 1.5 mg/kg, given in a single daily dose can be used until serum CK has normalized, after which the prednisone is tapered slowly over a 12-month period.<sup>242</sup> Another regimen involves (1) oral prednisone in a divided daily dose of 40 to 60 mg/day (1-2 mg/kg in children) until the CK has normalized; (2) consolidation of the prednisone into a single daily dose, which is then reduced by one fourth every 3 to 4 weeks only if the CK value is still normal; and (3) continuation of the prednisone until a maintenance dose of 5 to 10 mg/day is reached, at which time this dosage is continued for 1 year.<sup>243</sup> Even if the CK value is within normal range, an increase relative to a previous value indicates that the prednisone should not be tapered and should possibly be increased. Relying solely on CK levels is not wise, however, because a minority of patients can have an increase in CK without progression of muscular weakness.<sup>244</sup> Initial treatment with every-other-day steroids is not advised because there is a higher incidence of relapse.<sup>245</sup> The course of prednisone treatment can be divided into monocyclic, polycyclic, and chronic polycyclic, and initial relapses usually occur after 2 years of initiation of therapy.<sup>246</sup> Objective improvement in muscle strength is usually seen by the third month of therapy, but, if no progress is noted by this time, which occurs in up to 25% of patients, other immunosuppressive therapy should

be considered.<sup>26,247</sup> One study of 113 patients with definite myositis demonstrated that one third of patients with a short delay to diagnosis responded completely to prednisone, whereas no patients with a long delay did.<sup>121</sup> Another study demonstrated that clinical muscle strength improvement usually lags behind decreasing CK values.<sup>35</sup> Initial pulsed intravenous methylprednisolone treatment has been used in children with good results (30 mg/kg per dose for 3 days, then as needed for 4-5 weeks), followed by oral prednisone.<sup>248-252</sup>

Long-term use of prednisone can result in steroid myopathy, which mimics worsening dermatomyositis and polymyositis, and both processes can coexist.<sup>241,253</sup> Selective atrophy of type II muscle fibers in steroid myopathy can manifest clinically with progressive weakness despite normalization or no increase in CK values.<sup>244</sup> Reduction of neck flexor strength is usually seen in the natural progression of the disease and can be used to distinguish between the two causes. A review of the patient's strength, other medical conditions, CK levels, and prednisone dosages in the previous 4 to 8 weeks as well as possible drug side effects may be helpful, but a trial increase or decrease of corticosteroids may prove diagnostic within 2 to 8 weeks.<sup>241</sup>

### Immunosuppressive and steroid-sparing agents

**Methotrexate.** Methotrexate is the first-line adjuvant therapy in dermatomyositis or polymyositis recalcitrant to steroids, and clinical improvement can be seen in the majority of patients.<sup>32,254</sup> It was first used in the treatment of these diseases in 1971.<sup>255</sup> In one study that used methotrexate to treat children unresponsive to prednisone, the dosage of 20 mg/m<sup>2</sup> was used, increased muscle strength occurred in all participants at a median of 35 weeks after initiation of therapy, the CK level normalized in all 6 patients with initially elevated levels, and almost all were able to taper their prednisone dosage to less than 5 mg/day.<sup>256</sup> However, in almost one third of the participants, the drug had to be stopped because of severe abdominal pain, elevated liver function tests, decreased pulmonary diffusion capacity, or opportunistic infections. Similar responses in the adult population have also been seen.<sup>32</sup> The dosage should be started at 7.5 to 10 mg per week, increasing by 2.5 mg increments up to a total

dosage of 25 mg per week when given orally or 10 mg originally, increasing by 2.5 mg up to 0.5 to 0.8 mg/kg when given intravenously.<sup>243,247,255</sup> In children 1 mg/kg or 20 mg/m<sup>2</sup> has been used successfully.<sup>254,256</sup> While the methotrexate dosage is increased, prednisone should be tapered. Side effects of methotrexate usage include stomatitis, hepatic fibrosis and cirrhosis, nausea, abdominal pain, neutropenia, pruritus, fever, pneumonitis, and gastrointestinal symptoms.<sup>247,254</sup> One to 3 mg of daily folic acid can be used to minimize side effects without sacrificing efficacy. A pretreatment liver biopsy is appropriate if the patient has underlying liver disease.

**Azathioprine and cyclophosphamide.** In one of the few prospective, double-blind trials of drug therapy for myositis, azathioprine plus prednisolone offered long- but not short-term (< 3 months) benefit to patients with polymyositis relative to patients treated with steroids alone.<sup>257,258</sup> The dosage is 2 to 3 mg/kg per day and can be tapered to 1 mg/kg per day once the daily prednisolone is reduced to 15 mg or less per day. The usual dosage of azathioprine is 100 to 200 mg/day. Monthly reductions in dosage should be done in 25-mg intervals, with the expectation of maintaining the patient on a regimen of 50 mg/day. Adverse effects include increased risk of lymphoma, nausea and vomiting, hepatotoxicity, leukopenia from bone marrow suppression, and oral ulcerations.<sup>24,259</sup> Screening patients for homozygous or heterozygous thiopurine methyltransferase deficiency (occurring in 0.3% and 11% of the Caucasian population, respectively), one of two enzymes that catabolize azathioprine, can reduce the chance of toxicity associated with the use of the drug.<sup>260</sup>

Cyclophosphamide has not been as beneficial as azathioprine in treatment of myositis. Its place in the treatment of dermatomyositis is in cases refractory to the above medications because it alone does not usually treat myositis adequately.<sup>261,262</sup> However, some studies have shown benefit.<sup>263,264</sup> One patient with Sjögren's syndrome and polymyositis benefited solely from cyclophosphamide.<sup>265</sup> Cyclophosphamide has been added to prednisone with much improvement in patients with myositis and interstitial pulmonary disease.<sup>266</sup> Prednisone in combination with methotrexate and cyclophosphamide or chlorambucil can be used in severe disease not responding

to the usual medications.<sup>267,268</sup> Oral cyclophosphamide can be used at 1 to 3 mg/kg per day or intravenous administration at 2 to 4 mg/kg per day in conjunction with prednisone.<sup>269</sup> The potential side effects also make this medication less desirable: increased risk of malignancy (lymphoma, leukemia, bladder carcinoma, and squamous cell carcinoma), leukopenia, hemorrhagic cystitis, anorexia, nausea, vomiting, alopecia, and stomatitis.<sup>270</sup>

**Cyclosporine.** Cyclosporine impairs T-cell proliferation by blocking transcription of cytokine-encoding genes (such as interleukin-2) by inhibiting calcium-dependent T-cell activation.<sup>271</sup> In the early 1980s, cyclosporine was first used for myositis unresponsive to conventional therapy.<sup>272</sup> In one of the earlier studies, 14 children with longstanding disease were able to drastically reduce or stop their prednisone, with concomitant increase in muscle strength.<sup>273</sup> Cyclosporine has also been used as a single agent for initial treatment of myositis with excellent results.<sup>274</sup> Response to the medication can be as rapid as 1 week. Dosage reported in the literature is 2.5 to 10 mg/kg, although some studies suggest starting at or below 5 mg/kg and maintaining a whole blood level of 200 to 300 ng/mL.<sup>275</sup> Cyclosporine's many risks may limit the use of the drug in myositis, and these include nephrotoxicity, lymphomas, hypertension, hypertrichosis, gingival hyperplasia, hepatotoxicity, paresthesias, hyperesthesias, fatigue, and depression.<sup>270</sup>

### Hydroxychloroquine

Hydroxychloroquine can be used as an adjunctive treatment and has been consistently reported to reduce the rash of dermatomyositis recalcitrant to steroids and other treatment modalities.<sup>95,276,277</sup> However, studies differ in specific regard to the efficacy of hydroxychloroquine as a steroid-sparing agent in the treatment of the myositis and weakness. Daily dosage is 200 mg twice a day for adults and 2 to 5 mg/kg per day in children. It has been reported that hydroxychloroquine and chloroquine can cause a myopathy that is almost indistinguishable from inflammatory myopathies on electromyography, but can be distinguished by histopathologic examination of muscle tissue.<sup>112</sup>

### Intravenous immunoglobulins

In a double-blind, placebo-controlled trial in patients with therapy-resistant dermatomyositis,

intravenous immunoglobulins administered at 2 gm/kg in a divided dose, once per month for 3 months, offered significant improvement in more than 70% of patients.<sup>278,279</sup> Muscle biopsy specimens taken after treatment compared with those done before treatment demonstrated an increase in muscle fiber diameter, increased number and decreased size of capillaries, resolution of complement deposition on capillaries, and decreased intercellular adhesion molecule-1 and MHC1 antigens. Studies with juvenile myositis, at a dose of 1 to 2 gm/kg per day twice monthly for 9 months, have also proved the efficacy of intravenous immunoglobulin.<sup>280-282</sup> The purported effectiveness most likely occurs because of decreased complement deposition secondary to blockade of the Fc receptor on vascular walls and decreased synthesis of membrane attack complexes from activated C4b and C3b fragments, inhibition of T cells from releasing cytokines and lymphokines, and down-regulation of immunoglobulin production. The realistic use of intravenous immunoglobulins in patients with myositis may be limited by the high cost of the medication.

#### Other treatment modalities

**Total body irradiation.** Total body irradiation has been used as a last-ditch effort in severely recalcitrant disease, although most of the information about this mode of therapy has been culled from case reports.<sup>283-285</sup> Usually 15 rad is given biweekly over a 5-week period for a total of 150 rad. The side effects include pancytopenia, death, and lymphoma, and the treatment is certainly not uniformly curative.<sup>286</sup>

**Thymectomy.** Thymectomy has been used in only a small number of patients.<sup>287,288</sup> One case report describes a patient who was refractory to corticosteroids and plasmapheresis and who not only started improving after 4 weeks of thymectomy, but also was off all medications within 2 years.

**Plasmapheresis.** Plasmapheresis reduces the amount of circulating antibodies and cytokines; it has also been reported to offer major or moderate improvement in muscle weakness in case reports of juvenile and adult dermatomyositis<sup>289,290</sup> and in two thirds of 21 patients, most of whom had juvenile dermatomyositis.<sup>291</sup> One study demonstrated improvement in 91% of previously unresponsive patients, but these patients were concomitantly administered cyclophosphamide, chlorambucil,

and/or prednisone.<sup>292</sup> However, one prospective double-blind study demonstrated no improvement relative to sham apheresis.<sup>293</sup>

#### PROGNOSIS

In an effort to delineate prognostic indicators in dermatomyositis, studies have attempted to identify independent risk factors predicting a poor outcome. Because more aggressive treatment with immunosuppressive agents has become the standard of care, mortality rates have decreased significantly. In analyses of populations reflecting the spectrum of inflammatory myositis, poor indicators include recalcitrant disease, delay to diagnosis and therapy, older age, malignancy, fever, asthenia-anorexia, pulmonary interstitial fibrosis, dysphagia, and leukocytosis.<sup>294,295</sup> One study of 69 patients described survival rates of 83% at 1 year, 74% at 2 years, 67% at 5 years, and 55% at 9 years, with the most common causes of death being malignancy and cardiac, pulmonary, and iatrogenic complications. On the basis of steroid trials per year as well as duration without immunosuppressive therapy, myositis with associated connective tissue disease has a statistically better prognosis than all other types of inflammatory myositis.<sup>42</sup> Determination of myositis-specific autoantibodies can also aid in placing patients into prognostic categories. Those with anti-SRP, anti-synthetase, and anti-Mi-2 autoantibodies have poor, moderate, and good response to steroid therapy, respectively (see Table IV).

In juvenile dermatomyositis, initial treatment with low-dose prednisone, late onset of treatment, recalcitrant disease and pharyngeal involvement are poor indicators, with two thirds of children in this group having severe complications of calcium deposition.<sup>33,38</sup> In the United States, the current mortality rate for children is 3%.<sup>79</sup>

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## Answers to CME examination

Identification No. 898-111

November 1998 issue of the Journal of the American Academy of Dermatology

Questions 1-32, Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. *J Am Acad Dermatol* 1998;39:667-87.

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|------|-------|-------|-------|
| 1. c | 9. b  | 17. c | 25. d |
| 2. e | 10. a | 18. a | 26. c |
| 3. a | 11. a | 19. b | 27. a |
| 4. b | 12. a | 20. a | 28. d |
| 5. c | 13. d | 21. c | 29. b |
| 6. a | 14. d | 22. d | 30. a |
| 7. a | 15. d | 23. b | 31. c |
| 8. c | 16. e | 24. b | 32. e |

## CME examination

Identification No. 898-112

Instructions for Category I CME credit appear in the front advertising section. See last page of Contents for page number.

Questions 1-30, Kovacs SO, Kovacs SC. *J Am Acad Dermatol* 1998;39:899-920.

*Directions for questions 1-16: Give single best response.*

1. In approximately what proportion of adult patients with an inflammatory myopathy do skin manifestations develop?
  - a. 10% to 20%
  - b. 30% to 40%
  - c. 50% to 60%
  - d. 70% to 80%
  - e. 90%
2. Which one of the following statements is false?
  - a. Juvenile dermatomyositis has a bimodal age distribution.
  - b. Amyopathic dermatomyositis is more common in the adult population.
  - c. African-Americans are predominantly affected with dermatomyositis with or without malignancy.
  - d. There is a female preponderance in most studies of patients with dermatomyositis.
  - e. Ninety-five percent of children with an inflammatory myopathy have skin manifestations.
3. The most common skin manifestation in dermatomyositis is
  - a. periungual telangiectases
  - b. erythematous-lilac heliotrope macular rash with periorbital edema
  - c. Gottron's papules and Gottron's sign
  - d. erythema on sun-exposed skin
  - e. mechanic's hands
4. Which of the following descriptions of muscular signs or symptoms in patients with dermatomyositis/polymyositis (DM/PM) is true?
  - a. Dysphagia is an uncommon symptom.
  - b. Weakness is usually acute.
  - c. Cardiac palpitations, falling, and muscular atrophy are more common in patients with dermatomyositis than in those with polymyositis.
  - d. The more extensive the skin manifestations, the worse the disease activity.
  - e. Deep tendon reflexes are unchanged.
5. Which of the following statements regarding juvenile dermatomyositis is false?
  - a. Electrocardiographic abnormalities are seen in 50% of all patients.
  - b. Gower's sign reflects truncal weakness.
  - c. Low-grade fever is an uncommon symptom.
  - d. A marked reduction in osteocalcin production has been demonstrated.
  - e. There is no association between malignancy and juvenile dermatomyositis.
6. In specific regard to amyopathic dermatomyositis,
  - a. histopathologic characteristics of the skin are a sensitive but not a specific indicator of disease.
  - b. incidence is approximately 25% of DM/PM cases.
  - c. calcium deposition occurs in the majority of patients.
  - d. magnetic resonance imaging should never be used.
  - e. abnormal muscle activity is never demonstrated.
7. The least likely connective tissue disease to be associated with DM/PM is
  - a. systemic lupus erythematosus
  - b. rheumatoid arthritis
  - c. polyarteritis nodosa
  - d. mixed connective tissue disease
  - e. ankylosing spondylitis
8. Patients with DM/PM associated with a connective tissue disease
  - a. usually have myositis that responds better to corticosteroids than do dermatomyositis patients without a connective tissue disease
  - b. demonstrate the slight female preponderance seen in patients with dermatomyositis
  - c. usually present with muscle weakness and myalgias
  - d. usually manifest dermatomyositis over polymyositis
  - e. are less likely to demonstrate positive non-myositis-specific antibodies
9. Which of the following muscle enzymes is the most sensitive indicator of DM/PM?
  - a. Serum glutamic-oxaloacetic transaminase
  - b. Serum glutamic-pyruvate transaminase
  - c. Alanine aminotransferase
  - d. Creatine kinase
  - e. Lactate dehydrogenase
10. Myositis-specific antibodies
  - a. are seen in approximately 10% of patients with DM/PM
  - b. are seen more commonly in patients with DM/PM associated with malignancy
  - c. do not correlate with disease activity
  - d. tend to precede the onset of myositis
  - e. are directed against nuclear proteins

11. Patients who present with dermatomyositis should have all but one of the following tests done:
  - a. Chest roentgenography
  - b. Muscle enzymes
  - c. Stool guaiac
  - d. Urinalysis
  - e. Computed tomographic scan
12. Systemic lupus erythematosus (SLE) is different from dermatomyositis in all of the following ways *except*
  - a. SLE usually has a significantly positive antinuclear antibody.
  - b. dermatomyositis has a higher incidence of pruritus.
  - c. SLE demonstrates C5b-9 membrane attack complexes more frequently than does dermatomyositis in lesional skin biopsy specimens.
  - d. the eruption of dermatomyositis is more violaceous and less pink than that in SLE.
  - e. the skin manifestations of SLE tend to involve the malar eminences more than periorbital areas.
13. Each of the following pathologic processes should be included in the differential diagnosis of DM/PM *except*
  - a. trichinosis
  - b. HIV infection
  - c. hypothyroidism or hyperthyroidism
  - d. subacute lupus erythematosus
  - e. cyanide toxicity
14. Each of the following drugs has been implicated in producing a characteristic dermatomyositis syndrome *except*
  - a. penicillamine
  - b. phenylbutazone
  - c. hydroxyurea
  - d. aspirin
  - e. provastatin
15. Which of the following statements is true?
  - a. Intravenous methylprednisone treatment has been used in children with good results.
  - b. Selective atrophy of type II muscle fibers in dermatomyositis can manifest clinically with progressive weakness.
  - c. In the differentiation of steroid-induced myopathy from DM/PM, reduction of neck flexor strength is usually noted in the former condition.
  - d. Surgical intervention in patients with severe calcinosis can lead to severe complications and should not be recommended.
  - e. Cyclophosphamide has been more beneficial than azathioprine in the treatment of DM/PM.

16. Indicators reflecting a poor prognosis include each of the following *except*
  - a. asthenia-anorexia
  - b. myositis associated with a connective tissue disease
  - c. fever
  - d. dysphagia
  - e. leukocytosis

*Directions for questions 17-24: For each numbered item, choose the appropriate lettered item.*

- a. True
  - b. False
17. Muscle pain in the acute form of the disease is common.
  18. Histopathologic examination of muscle in a patient with dermatomyositis demonstrates a fascicular/ endomysial inflammation pattern.
  19. Both dermatomyositis and polymyositis have increased CD3<sup>+</sup> mononuclear cells in peripheral cytopathology analysis.
  20. Calcinosis cutis in the juvenile dermatomyositis population is associated with overall disease activity.
  21. The majority of patients with dermatomyositis initially present with skin changes only.
  22. Low-titer antinuclear antibody positivity occurs in the majority of adults with DM/PM and a minority of children with juvenile dermatomyositis.
  23. Hydroxychloroquine effectively treats the dermatomyositis rash.
  24. An individual patient can express more than one myositis-specific antibody.

*Directions for questions 25-30: For each numbered item, choose the appropriate lettered item.*

- a. Anti-FER autoantibody
  - b. Anti-Ku autoantibody
  - c. Anti-Jo-1 autoantibody
  - d. Anti-SRP autoantibody
  - e. Anti-Mi-2 autoantibody
25. Has the best response to steroids and best prognosis relative to the other myositis-specific autoantibodies
  26. Also known as histidyl-tRNA synthetase
  27. Highly specific for polymyositis
  28. Acute winter onset, severe muscle weakness and myalgias, and cardiac palpitations
  29. Mechanic's hands, arthritis, fevers, Raynaud's phenomenon, and carpal tunnel syndrome
  30. Most highly specific for dermatomyositis